

AMENDMENTS TO THE SPECIFICATION

On page 1, line 24, please replace the original paragraph with the following amended paragraph:

The RNA hydrolytic enzyme simply composed of a DNA is generally referred to as a DNA enzyme (deoxyribozyme, DNAzyme), and is an artificial ribonuclease developed by an in vitro selection method. Since an in vivo metal, Mg²⁺, serves as a cofactor, an in vivo application is possible. Specific contents thereof are disclosed in Non-patent Document 1. An 8-17 DNA enzyme (SEQ ID NO: 10) and 10-23 DNA enzyme (SEQ ID NO: 11) are included, and sequence formulae thereof are as described below.

On page 2, line 10, please replace the original paragraph with the following amended paragraph:

In the above-described sequence formulae, arrows indicate cleavage sites. The base sequence of the substrate RNA at the cleavage site is GA for the 8-17 DNA enzyme, and is Y(U or C)R(A or G) for the 10-23 DNA enzyme. The sequence of the DNA enzyme becomes a sequence complementary to the substrate RNA. However, CCGAGCCGGACGA (sequence number SEQ ID NO: 1) in the 8-17 DNA enzyme and GGCTAGCTACAACGA (sequence number SEQ ID NO: 2) in the 10-23 DNA enzyme are catalytically active loops, and are not complementary to the substrate RNA.

On page 18, line 13, please replace the original paragraph with the following amended paragraph:

Finally, a chemically modified DNA enzyme including an azobenzene derivative, according to the present invention, was synthesized. In the present example, a 10-23 DNA enzyme was synthesized. For the synthesis of the chemically modified DNA enzyme, ABI394 type DNA synthesizer was used, phosphoamidite monomers XI(a) to XI(c) produced as described above and a commercially available phosphoamidite monomer corresponding to four natural bases were used, and DNA enzymes (DNA-1A: sequence number SEQ ID NO: 4, DNA-1B: sequence number SEQ ID NO: 5, and DNA-1C: sequence number SEQ ID NO: 6) of the present invention having the following base sequences were synthesized. After unrefined products were produced on the basis of an usual protocol, the resulting unrefined products were refined by conducting gel refinement and high performance liquid chromatography refinement. For a comparative example, a DNA enzyme (DNA-N: sequence number SEQ ID NO: 3) simply composed of four natural bases was synthesized in a manner similar to that described above. Each base sequence is shown in the following Table 1. In the base sequences, the underlined base sequences represent catalytically active loops.

On page 19, line 8, please replace the original paragraph with the following amended paragraph:

[Table 1]

DNA enzyme	Base sequence
DNA-N (sequencee number <u>SEQ ID</u> <u>NO:</u> 3)	5' – CTGAAGGGGG <u>C</u> TAGCTACAA <u>CG</u> ATTCTTCCT – 3'
DNA-1A (sequencee number <u>SEQ ID</u> <u>NO:</u> 4)	5' – CTGAAGGGGG <u>C</u> TAGCTACAA <u>CG</u> A <u>X</u> _A TTCTTCCT – 3'
DNA-1B (sequencee number <u>SEQ ID</u> <u>NO:</u> 5)	5' – CTGAAGGGGG <u>C</u> TAGCTACAA <u>CG</u> A <u>X</u> _B TTCTTCCT – 3'
DNA-1C (sequencee number <u>SEQ ID</u> <u>NO:</u> 6)	5' – CTGAAGGGGG <u>C</u> TAGCTACAA <u>CG</u> A <u>X</u> _C TTCTTCCT – 3'

On page 20, line 3, please replace the original paragraph with the following amended paragraph:

5'-(FITC)-AGGAAGAAGCCUUCAG-3' (sequence number-SEQ ID NO: 7)

On page 20, line 6, please replace the original paragraph with the following amended paragraph:

The DNA enzymes (DNA-N: sequence number-SEQ ID NO: 3, DNA-1A: sequence number-SEQ ID NO: 4, DNA-1B: sequence number-SEQ ID NO: 5, and DNA-1C: sequence number-SEQ ID NO: 6) synthesized in Synthesis example 1 were used. The RNA cleavage experiment was conducted in accordance with the following procedure. First, 4 µL of DNA enzyme aqueous solution, 4 µL of substrate RNA aqueous solution, and furthermore, 4 µL of

buffer aqueous solution were taken into a microtube, and agitation and mixing were conducted adequately at room temperature. The final concentration of each substance contained in the reaction solution was adjusted as described below.

On page 21, line 1, please replace the original paragraph with the following amended paragraph:

Next, the resulting reaction solution was transferred to a constant temperature bath adjusted at 37°C, and reaction was conducted for 1 hour with respect to Comparative example 1 (DNA-N: sequence number SEQ ID NO: 3) and Examples 1 and 2 (DNA-1A: sequence number SEQ ID NO: 4 and DNA-1B: sequence number SEQ ID NO: 5), and for 40 minutes with respect to Example 3 (DNA-1C: sequence number SEQ ID NO: 6). Thereafter, 12 µL of aqueous solution containing 10 mol/L of urea and 50 mmol/L of ethylenediaminetetraacetic acid was added to terminate the reaction, and cleavage pieces of the RNA and uncleaved RNA were separated by acrylamide gel electrophoresis. Finally, FITC in the resulting gel was excited by the light of 470 nm and the fluorescence intensity at 520 nm was monitored with a fluorimeter (FLA-3000: produced by Fuji Photo Film Co., Ltd.), so that the amount of cleavage of the RNA was quantified. The cleavage results are shown in the following Table 2.

On page 22, line 1, please replace the original paragraph with the following amended paragraph:

[Table 2]

	DNA enzyme	Amount of cleavage (%)
Comparative example 1	DNA-N (sequence number <u>SEQ ID NO: 3</u>)	12.5
Example 1	DNA-1A (sequence number <u>SEQ ID NO: 4</u>)	38.8
Example 2	DNA-1B (sequence number <u>SEQ ID NO: 5</u>)	36.0
Example 3	DNA-1C (sequence number <u>SEQ ID NO: 6</u>)	33.3

On page 23, line 3, please replace the original paragraph with the following amended paragraph:

[Table 3]

DNA enzyme	Base sequence
DNA-2A (sequence number <u>SEQ ID NO: 8</u>)	5' - CTGAAGGGGG <u>C</u> TAGCTACAA <u>ACGATX</u> _A TCTTCCT - 3'
DNA-3A (sequence number <u>SEQ ID NO: 9</u>)	5' - CTGAAGGGGG <u>C</u> TAGCTACAA <u>ACGATT</u> _X _A TTCCT - 3'

On page 24, line 4, please replace the original paragraph with the following amended paragraph:

[Table 4]

	DNA enzyme	Amount of cleavage (%)		Reaction time
		Under UV light irradiation	No UV light irradiation	
Comparative example 2	DNA-N (sequence number <u>SEQ ID NO: 3</u>)	37.3	37.6	4 hours
Example 4	DNA-1A (sequence number <u>SEQ ID NO: 4</u>)	12.4	38.8	1 hour
Example 5	DNA-1B (sequence number <u>SEQ ID NO: 5</u>)	21.7	39.0	1 hour
Example 6	DNA-2A (sequence number <u>SEQ ID NO: 8</u>)	18.0	29.4	4 hours
Example 7	DNA-3A (sequence number <u>SEQ ID NO: 9</u>)	12.3	18.5	4 hours

Please insert Sequence Listing, enclosed herewith, immediately after the abstract.